REMARKS

Claims 23-26, 28, 30-33, 35, and 37-43 are currently under consideration. Claims 23, 25, 30, 35, 37 and 42 have been amended for the purpose of expediting prosecution. The "new matter" rejections discussed in an interview 7 June 2005 are discussed immediately below under the headers from the outstanding Final Rejection. New Claim 43 has been added and finds support in the application at page 15, line 7.

Priority

The Examiner has objected to the language "and mixtures thereof" as changing the scope of Claim 23, and the phrase has therefore been deleted. Accordingly, this case remains a division of the parent patent.

Specification

The Examiner has objected to the phrase added to the paragraph that starts on page 13, line 26 as new matter. The language, "where the DNA further includes one or more stop codons in one or more reading frames of the integrase gene" is found in Claim 7.

Claim Objections

The Examiner has objected to the Markush format of Claim 35 and suggested an amendment. This amendment has been incorporated herein.

Claim Rejections – 35 USC § 112

A second new matter rejection has been made to Claim 23 with respect to the scope of "antigen presenting cells." Support for this genus is found at page 11, lines 10-22, and page 12, lines 25-27. The examiner has objected to "of the skin" because the cells may be found in other places (blood). The examiner has objected to the word "animal" which is supported by Claims 17 and 19; and applying the complex to the "skin or mucosa surfaces;" this language is supported at page 16, line 34.

The Examiner has objected to Claim 25 with respect to the genus "polyethylenimine derivatives that target a receptor found on the surface of antigen presenting cells." This language is supported at page 21, lines 8-10 (multiple sugars, dendritic cells) and page 11, lines 16-17 (other kinds of cells). Claim 25 has also been amended to correct a typographic error in the chemical name.

The Examiner has objected to Claim 27 with respect to the language mannosylated PEI "derived from a linear PEI 22 kDA; this claim has been cancelled.

The Examiner has objected to the range in Claim 29, which has been cancelled.

The Examiner has objected to Claim 42 as containing new matter and being unclear, because page 22, lines 9-16 taught the ratio of 3:1 was not used in the method of the invention. However, the applicant points out that at page 22, line 12, shows that the ratio of 3:1 (N:P) PEI-DNA was used, and has a neutral charge, and this ratio is in contrast to the ratio of 5:1 (N:P) for PEI-man:DNA that has the neutral charge in the line just above. Claim 30, which has not been objected to for lack of clarity but which has a structure similar to Claim 42 has been amended in parallel to forestall the clarity objection.

The above amendments and remarks are intended to wholly reflect the discussion during the interview, and address all the Examiners questions and objections through the first paragraph of page 9 of the Final Rejection.

The following Remarks are offered to the outstanding Final Rejection

2. Rejections under 35 USC § 112, 1st para
Claims 23-33, 35 and 37-41

Claims 23-33, 35 and 37-42 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The Examiner states that the claims are drawn to transfecting antigen presenting cells (APCs) of the skin by applying a complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding a an immunogenic protein and ii) sugar, polyethylenimine (PEI), a PEI derivative, or mixture thereof.

The Examiner says the specification suggests using the method claimed to induce an immune response in a mammal (pg 20, Example 4) but states without citation that merely inducing an immune response in a mammal, in and of itself, does not have a use by itself because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the Examiner takes the position that inducing an immune response according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The Examiner adds that the methods using DNA encoding an immunogenic protein as claimed lack written description because the specification does not provide adequately describe *how to induce a therapeutic or prophylactic immune response* (emphasis added) using the method claimed.

The Examiner states that the applicants argue that the analysis of the claims by the examiner is in error because the claims merely require transfecting APCs and do not require a step in which therapy or prophylaxis is obtained. The Examiner states that the applicants' argument is not persuasive, because the claims must be read in light of the specification, and the only purpose for applying DNA encoding a protein from a lentivirus to the skin or mucosa of an animal is for therapy or prophylaxis. Therefore, the Examiner states that it is reasonable to determine whether the applicants have adequately described to those skilled in the art the steps required to applying DNA encoding a protein from a lentivirus to the skin or mucosa of an animal and obtain therapy or prophylaxis.

Response – Enablement/utility

Request for Interview with Supervisory Examiner and Customer Service Specialist

In response, the applicants enclose the following references: from the inventors, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the present invention to produce CTL responses; and Lisziewicz, et al., "Control of viral rebound through therapeutic immunization with DermaVir, which includes studies showing low toxicity, enhanced viral control, and longevity.

The applicants note that it is settled that the Examiner has not correctly stated the applicable law, which is set forth below, and that the USPTO is not free to evade the instructions is receives from the Federal Circuit. If this objection is not withdrawn now, the applicants must presume that the USPTO has made a policy decision to contravene the law recited below, and therefore request a copy of that decision, and also a meeting with the Examiner's Supervisor and the Customer Service Specialist.

With respect to the Examiner's requirement re therapeutic/prophylactic effect, the applicants note that there is no such limitation in the claims, and that the Examiner has stated a requirement inconsistent with the legal requirements. These Claims are supported by data showing the use of different DNAs, different compounds, complexes with varying properties, and targeting different receptors. They are supported by both *in vivo* and *in vitro* data in two different animal models. Both the parent patent and the current application contain data showing that genes have been delivered to antigen presenting cells, that the cells then both migrated to the lymph nodes, and expressed protein. *In vitro* CTL responses are reported, along with a report of a clinical result: a CTL response in an animal. In light of all this data, it is not understood how an enablement/utility rejection can be said to lie against this application, unless an examination standard is being applied that is different from those applied to the other technical arts.

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. Animal Legal Defense Fund v. Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985). The standard for enablement focuses on the person skilled in the art, Radomex, Inc. v. Scopus Corp., 7 USPQ2d 1050 (Fed. Cir. 1988) rather than the general public. For this reason, a specification is not required to teach what is known in the relevant art. Lindeman Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). Further, when a properly claimed invention meets at least one stated objective, utility under Section 101 is clearly shown.

Raytheon v. Roper, 220 USPQ 592 (Fed. Cir. 1983). For an issued patent to be held invalid for lack of utility under Section 101, the challenger must prove that the invention is totally incapable of achieving a useful result. Brooktree Corp. v. Advanced Micro Devices, Inc., 24 USPQ2d 1403, 1412 (Fed. Cir. 1992). The utility requirement is met where *in vitro* evidence indicates that positive *in vivo* results are likely. Cross v. Iizuka, 224 USPQ 739, 742-43 (Fed. Cir. 1985). Human clinical trials are not required, In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) and the PTO should not confuse the standard for patentability with the standard for FDA approval id., at 1442.

In this case, the requirement to show a therapeutic/prophylactic response is clearly inapplicable, and the conversion of the utility rejection to an enablement rejection does not undermine the applicable law or change the facts. The enablement/utility objections find their application in discouraging filings based on hypothetical examples and in cases of fraud, such as In re Oberweger, (baldness cure) 47 USPQ 455, 457 (CCPA 1940), but not more credible cases. See USPN 4,139,619 issued February 13, 1979 for a method of stimulating hair growth by topical application of minoxidil, and note that the text refers to another patent for the method of making the active ingredient in a series of formulations, and for experimental support. The present application contains clear experimental support for the amended Claims, and therefore the present objection must be withdrawn at this time.

Claim 23 – Written Description

The Examiner states that the genus of antigen presenting cells (APCs) in claim 23 lacks written description, and states that the specification as originally filed did not contemplate transducing any APCs other than dendritic cells. The Examiner states that the species of dendritic cells is not adequate to support the genus of APCs.

Response: Claim 23 – Written Description

The genus antigen presenting cells is specifically supported at page 12, lines 25-27, and page 11, lines 9-17.

Claims 23 and 37-39 – Written Description

The Examiner states that Claims 23 and 37-39 require using DNA encoding a protein from a lentivirus (23), specifically an HIV virus (37), more specifically from a replication-defective HIV virus (38), more specifically an integration-defective, replication-defective HIV virus (39). The Examiner states that the specification does not enable one of skill to use DNA encoding a lentiviral protein [to] transfect APCs *and treat or prevent disease*. (emphasis added). The Examiner states that the Applicants describe using plasmids encoding replication-defective, integrase-defective retroviral DNA in related application 08/989,301 as being non-lethal and capable of inducing a therapeutic/prophylactic immune response when administered in vivo. However, the Examiner points to an earlier reference cited Adachi (J. Virol., Aug. 1986, Vol. 59, pg 284-291) taught such viruses were still infectious. The Examiner states that DNA encoding a lentiviral protein, specifically DNA encoding a "replication defective retroviral" protein that is non-lethal and capable of

inducing a therapeutic/prophylactic immune response, is not adequately described by applicants. *Nowhere have applicants provided any evidence that the amount of expression of viral protein is adequate to induce a therapeutic/prophylactic immune response or that the virus does not replicate too much and cause disease.* (emphasis added). The Examiner speculates that use of the plasmids encoding replication-defective retrovirus in animals as claimed would not treat or prevent disease because the virus would replicate and cause disease. The Examiner states that, contrary to the disclosure of the application, the applicants appear to be attempting to find DNA comprising a lentiviral protein that expresses adequate viral protein such that a cellular immune response can be obtained, wherein said DNA i) does not make retroviral particles or ii) does make viral particles that replicate to a low degree without causing disease. The Examiner adds that naming a type of material that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using replication-defective retroviruses without defining what means will induce a therapeutic/prophylactic effect without causing infection is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)).

The Examiner states that the applicants argue that the examiner has mischaracterized claims 36-39. The Examiner states that the examiner's discussion of retroviruses is misplaced because retroviruses have RNA while the instant claims require DNA. The Examiner states that the applicants' argument is wholly unfounded. While retroviral particles have RNA, retroviral DNA is used to transfect packaging cells and make the retroviral particles comprising RNA. The specification describes using constructs comprising DNA encoding replication or integration defective HIV (pg 13, lines 26-30). Therefore, the DNA in claims 36-39 can be transcribed into RNA and made into retroviral particles upon division of the transfected cell. As such, it is reasonable to conclude that claim 23 encompasses transfecting APCs in an animal with DNA encoding lentiviral proteins resulting in lentiviral particle formation (comprising RNA) and lentiviral infection, *wherein the protein induces an immune response but the retroviral particles do not replicate too much and cause disease.* (emphasis added) This DNA encompassed by claim 23 and described vaguely by the applicant lacks written description for reasons above because the structure having the function has not been described.

Response – Written Description, Claims 23, and 37-39

The present application is not directed to the construction of a specific replication-defective retrovirus. It relates to a new method for transfecting antigen presenting cells. One of the advantages of the claimed invention is that it converts materials that have been previously unusable into a viable form. The present language is supported at page 13, lines 27-36, and it is noted that USSN 08/803,484, which extensively discusses replication-defective viruses that can be used as templates for the artificially made plasmids, is incorporated by reference as if set forth in full. Replication-defective viruses are known in the art, and one of ordinary skill in the art would also recognize the difference between a viral particle and a plasmid encoding the same. The standard for enablement focuses on the person skilled in the art, Radomex, Inc. v. Scopus Corp., 7 USPQ2d 1050 (Fed. Cir. 1988) rather than the general public. For this reason, a specification is not required to teach what is known in the relevant art. Lindeman Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). Moreover, the claimed invention has

been used to produce recognizable therapeutic effects, see the Lisziewicz references discussed, above. The Examiner's technical questions about the differences between a replication-defective retroviral particle and plasmid DNA encoding the same, are addressed in another article, Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells J Virol. Aug 2001, p. 7621-7628, where expression of viral antigen by plasmid DNA is compared to that of the replication-defective control in primary human lymphocytes, macrophages, and dendritic cells in Fig. 1 b-d.

Claim 23 – written description

The phrase "PEI, PEI derivatives and mixtures thereof" in claim 23 lacks written description. The specification does not contemplate combining PEI with derivatives of PEI or combining different derivatives of PEI. It is not readily apparent that applicants were in possession or even contemplated any "mixture thereof" as broadly claimed.

Response Claim 23 – written description

This objection is not applicable to the amended claims because "and mixtures thereof" has been deleted.

3. Rejections under 35 USC § 112, 1st para

Claims 23-33, 35 and 37-42

Claims 23-33, 35 and 37-42 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The claims are said to be drawn to transducing antigen presenting cells (APCs) of the skin by applying a complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding a an immunogenic protein from a lentivirus and ii) sugar, polyethylenimine (PEI), a PEI derivative, or mixture thereof.

The Examiner admits that the specification describes using the method claimed to induce an immune response in a mammal as claimed (pg 20, Example 4) [the applicants note that the immune response confirms that transfection has taken place, i.e., that the method works], The Examiner adds, without citation, that merely inducing an immune response in a mammal, in and of itself, does not have an enabled use *by law* (emphasis added) because inducing an immune response is only described in the specification as being used to obtain a *therapeutic or prophylactic effect* (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the Examiner states that inducing an immune response according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The Examiner states further that the ordinary artisan reading the claimed invention in view of the specification would only determine that the method claimed was for the purpose of therapy or prophylaxis. The Examiner concludes that applying DNA encoding an immunogenic protein to an animal as claimed is not enabled *because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response* (emphasis added) using the method claimed.

Further, the Examiner cites the Klatzmann and Sticker references, that are said to have taught retroviral vaccines have been unable to protect against infection (Katzmann, US Patent 6,140,114, Oct. 31, 2000; Stricker et al., Medical Hypotheses, June 1997, Vol. 48, pg 527-9). He cites a further article to show that, generally, a lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses (Bangham, Nov. 29, 1997, Lancet, Vol. 350, pg 1617-1621; pg 1617, top of Col. 1).

The Examiner admits that the specification teaches making plasmids encoding replication defective, integrase defective HIV as described in application 08/989,301 (pg 18, line 30-32). The Examiner states that, in application 08/939,301, applicants call such retroviruses "Class 4" viruses which are infectious but replication-defective (pg 15, lines 1-5). The Examiner says that, in application 08/989301, applicants teach that replication defective HIV that does not replicate effectively is inadequate to elicit a protective cellular immune response, or alternatively, that replication defective HIV that does replicate effectively causes disease and sometimes fatal (pg 3, line 17 through pg 4, line 3). The Examiner states his view of the problem, namely that the amount of replication of a retrovirus required to obtain a therapeutic cellular immune response without causing disease was unknown in the art at the time of filing, and that it was also unknown how to make a retrovirus with the adequate amount of replication that would provide an adequate cellular immune response without causing disease. The Examiner states that, without being able to make such a retrovirus, it was unknown how to use such a virus to obtain a therapeutic or prophylactic cellular immune response in a host.

The Examiner states that the specification does not provide adequate guidance regarding *how to obtain a therapeutic or prophylactic effect* by applying a replication defective retrovirus in an animal as claimed. The Examiner states that the specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus; the amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification; the amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification; the amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. The Examiner takes the position that, given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

The Examiner states that, in addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using in vivo or ex vivo gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, Ist ~, pg 65, 1 st T under Conclusion section; Verma, Sept. 1997, Nature, Vol, 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full para; pg 1789, col. 1, 1st para).

The Examiner states that the specification does not enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs *and obtain a therapeutic or prophylactic effect.* (emphasis added) It is unclear *how* (emphasis added) application of DNA to the mucosa would result in expression of the protein in the skin. The Examiner says that the specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. The Examiner states that, given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route

of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

The Examiner says that the applicants argue the analysis of the claims by the examiner is in error because the claims merely require transfecting APCs and do not require a step in which therapy or prophylaxis is obtained. Applicants' argument is not persuasive.

Response: The applicants have correctly stated the applicable law.

The Examiner says the claims must be read in light of the specification, that the only purpose for applying DNA encoding a lentiviral protein to the skin or mucosa of an animal is for therapy or prophylaxis; and that therefore, it is reasonable to determine whether applicants have provided adequate guidance for the sole disclosed use, i.e. whether applicants provide adequate guidance for those skilled in the art to apply DNA encoding a protein from a lentivirus to the skin or mucosa of an animal and obtain therapy or prophylaxis. The Examiner says that merely transfecting APCs with DNA encoding a lentiviral protein as in claim 23 *has no meaning without obtaining therapy or prophylaxis.*

The Examiner says the applicants argue a CTL response *in vitro* was obtained; therefore, applicants conclude the method can be used to obtain a therapuetic or prophylactic effect *in vivo*. Applicants' argument is not persuasive. First, any declarations filed in parent applications will have to be filed in the instant application to be considered. Second, the immune response required to treat or prevent lentiviral infection was not known (see references of record above). For example, HIV patients have a CTL response to the HIV virus that is not therapeutic or prophylactic. The art was and continues to be completely absent of methods to treat or prevent lentiviral infection *in vivo* using by inducing an immune response. The Examiner states that evidence of a CTL response *in vitro* does not overcome such unpredictability *in vivo*. Applicants have not provided any evidence in this case (or any other) that showed obtaining an immune response *in vivo*, specifically a therapeutic or prophylactic immune response.

Response: See Example 4, page 20, line 15 in the application. See Example 9, page 24, lines 15-26. See the enclosed journal articles.

Applicants have not provided any evidence that DNA expressed in viva was adequately expressed to induce an immune response. Applicants have not provided any evidence that inducing a CTL response in vivo against a lentiviral protein is *therapeutic or prophylactic* in view of the (uncited) overwhelming evidence to the contrary. The examiner says he is not requiring a showing or exemplification of inducing a therapuetic or prophylactic immune response using the method claimed; rather, the examiner is requiring a showing or exemplification of inducing a therapuetic or prophylactic immune response using the method claimed a reasonable teaching of the amount and type of protein to be expressed, the combination of promoter, protein and vector required to obtain adequate amounts of protein expression upon being applied to the skin or mucose, how to adequately target the proper number of APCs by applying DNA to the skin or mucosa, the proper number of APCs to be targeted and the immune response required to treat or prevent lentiviral infection. In this case, the applicants have provided neither a showing nor a reasonable correlation.

Response – Claims 23-33, 35 and 37-41

The applicants note that the Examiner has admitted that the invention as claimed is enabled. The Examiner admits he is adding a further requirement, for a showing that the transfection not only has occurred, and that an immune response has occurred, but also that

the immune response has a particular effect. As it happens, the applicants have such evidence, in the form of published articles, including Lisziewicz, et al., "Control of viral rebound through therapeutic immunization with DermaVir," studies showing low toxicity, enhanced viral control, and enhanced longevity. In the event this objection is not withdrawn, the applicants ask for a statement by the USPTO as to the law they are requiring the Examiner to apply, which apparently contravenes that of their supervisory court, together with a meeting with the Supervisory Examiner and the Customer Service Specialist.

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. Animal Legal Defense Fund v. Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985). The standard for enablement focuses on the person skilled in the art, Radomex, Inc. v. Scopus Corp., 7 USPQ2d 1050 (Fed. Cir. 1988) rather than the general public. For this reason, a specification is not required to teach what is known in the relevant art. Lindeman Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). Further, when a properly claimed invention meets at least one stated objective, utility under Section 101 is clearly shown. Raytheon v. Roper, 220 USPQ 592 (Fed. Cir. 1983). For an issued patent to be held invalid for lack of utility under Section 101, the challenger must prove that the invention is totally incapable of achieving a useful result. Brooktree Corp. v. Advanced Micro Devices, Inc., 24 USPQ2d 1403, 1412 (Fed. Cir. 1992). The utility requirement is met where *in vitro* evidence indicates that positive *in vivo* results are likely. Cross v. Iizuka, 224 USPQ 739, 742-43 (Fed. Cir. 19985). Human clinical trials are not required, In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) and the PTO should not confuse the standard for patentability with the standard for FDA approval id., at 1442.

In this case, the requirement to show a therapeutic/prophylactic response is clearly inapplicable especially in light of Example 4, which discloses a CTL response in an animal (page 20, line 15) and the discussion in Example 9, which places the results of the various experiments in context (page 24, lines 15-26. The enablement/utility objections find their application in discouraging filings based on hypothetical examples and in cases of fraud, such as In re Oberweger, (baldness cure) 47 USPQ 455, 457 (CCPA 1940), but not more credible cases. See USPN 4,139,619 issued February 13, 1979 for a method of stimulating hair growth by topical application of minoxidil, and note that the text refers to another patent for the method of making the active ingredient in a series of formulations, and for experimental support. The present application contains clear experimental support for the amended Claims, and therefore the present objection must be withdrawn at this time.

With respect to the Klatzmann and Stickler references, the Applicants note those references relate to the retroviral vaccines (not DNA) of others in totally different methods of gene delivery, and demonstrate failure of others. The Examiner's remark that there is overwhelming evidence that CTL responses are not therapeutic or prophylactic is not understood. The Examiner's requirement for other evidence appears to the applicants to be directed to what others have believed is necessary to make the inventions of other work, and is not germane to the present invention.

3. [sic]Rejections under 35 USC § 112, 2nd para
Claims 23-33, 35 and 37-41

Claims 23-33, 35 and 37-41 have been rejected under 35 U.S. C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 23 – "and mixtures thereof"

Claim 23 is said to be indefinite because it is said to be unclear whether "mixtures thereof' refers to mixtures of sugars, PEI and PEI derivatives or to mixtures of DNA with sugars, PEI or PEI derivatives.

Response: Claim 23 – "and mixtures thereof" and "of the Skin"

The applicants point out that the claim has been amended as suggested by the Examiner. To the extent the objection relates to the citation to the parent patent, the corresponding cites in the application are supplied herein. With respect to the objection to the body of the claim, it is noted that the method is directed to the transfection of antigen presenting cells, and that a given formulation is applied to the skin. No further physical steps on the part of the person using the invention to achieve transfections of the antigen presenting cells. The applicants are willing to insert a "whereby" clause, if that is what the Examiner is suggesting.

Claim 23 "Transfection"

Claim 23 as newly amended remains indefinite because it is unclear if "transfection" is limited to transfection with plasmid or if the term encompasses infection with a viral particle. The Examiner adds that the specification does not define "transfection".

Response: Claim 23 "Transfection"

The applicants note that this amendment was made in order to comply with what they thought was a demand by the Examiner. An objection to the original claim language "transducing" was not withdrawn in light of an explanation by the applicants, and so the claim was amended to the language the Examiner seemed to prefer. The applicants are open

to reasonable suggestions. For example, the language "Method of delivering genes into antigen presenting cells..."from the title of the application would be acceptable.

Claim 23 "applying to the skin"

Claim 23 is said to be indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. The Examiner states that it is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. The Examiner states that the applicants argue the claim excludes injections because they force fluid into a passage while "apply" is defined as to place in contact with, to lay or spread on. The Examiner states that the Applicants argument is not persuasive because subcutaneous injection results in the liquid going directly under the epidermis, i.e., the liquid in "in contact" with the skin.

Response: Claim 23 "applying to the skin"

This language is supported at page 16, line 34, where application to the skin is distinguished from injection.

Claim 27 – "derived"

Claim 27 is said to be indefinite because it is unclear what applicants consider a mannosylated PEI "derived" from a linear PEI 22kDA. The Examiner says that the metes and bounds of "linear" PEI cannot be determined. The phrase "a linear PEI 22kDN' is confusing because it is unclear if the linear PEI is 22kDA in weight or if PEI 22 kDA refers to some particular type of PEI.

Response: Claim 27 – "derived"

Claim 27 has been cancelled.

Claims 29 and 30 ranges

Claim 29 and 30 are said to be indefinite because the phrases "about 3-10:1 molar equivalent polyethylenimine or polyethylenimine derivate amine per DNA phosphate ratio" and "about 5:1 molar equivalent polyethylene mine or polyethylene mine derivate amine per DNA phosphate ratio" are said to be unclear. Page 22, lines 9-16, teaches that at the 5:1 (N:P) ratio, PEI-man-DNA is neutral. The specification states that N and P stand for nitrogen and phosphorus. It is unclear if the phrase is intended to be the limited to the ratio of polyethylenimine derivate amine per DNA phosphate or encompasses the ratio of polyethylene mine derivate amine or polyethylene mine amine per DNA phosphate. The Examiner comments that the phrase "molar equivalent polyethylenimine" seems to be missing a word making the phrase unclear. The metes and bounds of the phrase also cannot be determined because it is unclear what applicants consider "about 5 molar equivalents" of N and P.

Response Claims 29 and 30 ranges

These claims have been amended as discussed above, it is submitted that the present objection can be withdrawn.

Claim 31 "glucose solution"

Claim 31 is said to be indefinite because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man to a glucose+water or if the phrase encompasses PEI-glu, PEI-gal, or PEI-man + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompases adding PEI-glu to water to make a "glucose solution". The Examiner states that the applicant's arguments are noted but do not address the issue.

Response: Claim 31 – glucose solution

The Applicants point out that one of the surprising experimental results was that, the sugar-DNA complex, in the absence of PEI-mannose can transduce Langerhans cells *in vivo*, and that it outperformed DNA complexed with PEI. See application, page 24, lines 29-33. PEI-glucose-DNA also worked. See page 21, Table 1. So did PEI-DNA added to a glucose solution. See page 23, Table 2. The method of formulating the glucose solution appears to be immaterial. As a result, it does not matter whether the glucose solution is a solution in which the complex of claim 23 is put in or encompasses a complex made up of PEI conjugated with glucose, because both have been shown to work, and are within the scope of the invention. This language applies to both situations, and legitimately so. The very clear implication from these experiments is that the step where the PEI-glu complex is formed could be loaded with extra sugar so that, when water is added, a sugar solution results.

Claims 31 and 32 "about"

Claims 32 and 33 are said to be indefinite because the metes and bounds of the phrase "about 5-10% glucose" and "about 8% glucose" cannot be determined. The Examiner states that the specification does not teach how to determine the units of the 5-10% glucose described on page 22, line 35-36. Thus, the metes and bounds of the claims cannot be determined. The Examiner states the applicants have not addressed this issue.

Response: Claims 31 and 32 "about"

This objection is not applicable to the amended claims because the word was deleted in the last amendment.

Claim 34 "activating the antigen presenting cells"

The phrase "activating the antigen presenting cells" in claim 34 is said to be indefinite. According to the Examiner, it is unclear if the phrase is further limiting what happens when the complex is "applied" as in claim 23 or if it is a step that is separate from "applying" the complex that occurs before or after "applying" the complex. It is unclear if "activation" refers to expression of the immunogenic protein in the context of an MHC molecule or to a second, separate step that causes "activation" of the APCs, e.g. applying an interleukin that causes APC activation.

Response: Claim 34 "activating the antigen presenting cells"

This claim has been cancelled.

4. Claim Rejections - 35 USC § 102
Claims 23-32, 35, 40 and 41

Claims 23-32, 35, 40 and 41 have been rejected under 35 U,S,C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (USPN 5,679,647).

The parent application 60/058,933, does not describe complexing DNA with a compound selected from the group consisting of sugars, PEI, PEI derivatives, or mixtures thereof (claim 23). Therefore, the claimed invention does not get priorty back to 9-15-97. Parent application 09/153,198 (filed 9-15-98) does describe complexing DNA with PEI-mannose in a 5-10% glucose solution on page 26, lines 1-9. Therefore, claims 23-33, 35 and 37-43 have priority to 9-15-98.

Behr is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). The Examiner says Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals.

Response: The applicants note that luciferase is a commonly used marker gene, analogous to the gfp gene used in the experiments of the present application, and it was used in the reference simply as a marker gene, and no attempt was made to raise or measure an immune response or transfect APCs. Rather, light emission was measured after brain cells were transfected. (Col. 13, line 3).

Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1 –19).

Response: This reference merely says it can be done, but does not disclose how to do so. That is the applicants' invention.

Behr is said to have taught the DNA could encode an HIV peptide (Col. 3, lines 57-67). The Examiner comments that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art *because it may not occur*, then states that the method of Behr *inherently results in transfecting APCs* because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell," item 3).

Response: It appears to the applicant that the Examiner is refusing to accept the clear experimental results in this application, and at the same time crediting a bare disclosure that something "can be done" in a reference as full disclosure that a given result has been obtained.

The Examiner states he is not relying on the (new) Carson reference as a basis of the rejection, but says that the Carson reference is said to provide evidence that one of ordinary skill in the art would have had a reasonable expectation of successfully administering DNA to the skin and transfecting APCs (col. 36-37, Examples 11-12.)

Therefore, one of ordinary skill in the art would have had a reasonable expectation of successfully taking the teachings of Behr and transfecting APCs of the skin.

Response: The applicants do not understand how this reference can be used in a § 102 rejection. It is a new reference, and the Examiner is relying on it in what appears to be an obviousness rejection.

Claims 25-27 are included because they are not limited to a compound that is mannosylated PEI or PEI "derived from a linear PEI 22 kDA;" claims 25-27 encompass glucose as in parent claim 24.

Claims 28-30 are included because Behr taught that between 5-20 equivalents of PEI amines, are used relative to DNA phosphates (col. 8, lines 15-19), specifically 9 equivalents (col. 12, line 58). The instant specification teaches that such ratios cause the complex to be electrostatically neutral (para bridging pg 21-22).

Claim 33 is included because 5% is "about 8% as claimed.

Claims 34, 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Response–Claims 23-35, 40 and 41

The present application contains clear experimental support for the amended Claims, and therefore the present rejection must be withdrawn at this time. To anticipate a claim, a reference must teach every element of the claim. MPEP 2131. The applicants note that the Examiner impliedly admitted that the Behr reference has nothing to say about targeting antigen presenting cells, but instead has stated that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art *because it may not occur*. The applicants point out that the evidence that "transfecting antigen presenting cells" has occurred is in the text of this case and is copious.

Examples in the application present evidence that APCs were indeed transfected using the claimed method. Example 8 shows that the claimed complexes were applied to the skin of mice (page 22, line 37) and then skin samples were tested for transduction of Langerhans cells, and it was found that sugar modified gene delivery system is preferred to transduce antigen presenting cells. (page 23, lines 19-20). Example 9 shows that the claimed complexes also migrated to the lymph nodes and expressed protein (page 24, lines 6-7). Example 4 shows that the *ex vivo* procedure using APCs transfected *in vitro* produces a CTL response, and so the experiments, taken together, show that transcutaneous gene delivery with complexes (like PEI-man-DNA) can be utilized to generate immune responses against proteins encoded in the DNA. (page 24, lines 24-26)

The applicants also note that this is the type of preamble that should be given patentable weight, because it "breathes life and meaning into the claim" MPEP 2111.02. This limitation is directed to the *target cells*, which are disclosed to have a specific function

see page 11, lines 13-17, and page 12, lines 25-27 related to a specific physical structure (the mannose receptor: page 21, lines 8-9).

The Examiner has not pointed to any disclosure in the Behr reference of this class of target cells among the many classes listed. The Examiner does not point to any teaching of how to use this reference to select among the many different cell types. The Examiner's hypothetical example, where the Behr reference is said to inherently transfect APCs, would change the principle of operation of the Behr reference so substantially as to render it inoperative. It raises the possibility of obtaining an immune response (to be avoided, Col. 1, line 51) to a material needed for gene therapy (correction of a disorder resulting from a deficiency of a proteinaceous product Col. 6, lines 39-43). Further, the Examples in the current application present evidence that APCs were indeed transfected. Finally, the articles submitted herewith, demonstrate not only that the APCs are transfected, but that a therapeutic result is obtained. Any obviousness objection that might have been made by combining the uncited Carson reference with the Behr reference has been forestalled by this submission.

The applicants note that the present § 102 rejection was not withdrawn, and a Final Rejection issued, despite the applicants' incorporation of the limitations of a claim that the Examiner had admitted was not subject to the § 102 rejection. See MPEP 707(b). The applicants do not understand why this rejection was not withdrawn. That amendment was made solely for the purpose of expediting prosecution and securing issuance of this patent last year and is now withdrawn, because the reference has been distinguished on another basis.

5. Claim Rejections – 35 USC § 103

Claims 23-33, 35, 37, 38, 40 and 41

Claims 23-33, 35, 37, 38, 40 and 41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol, 59, pages 284-291) and Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97-107).

The Examiner states that the parent application provisional application No. 60/058,933 (9-1-97) does not describe complexing DNA with a compound selected from a group consisting of sugars, PEI, PEI derivatives (Claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% solution on pg 26, lines 1-9; therefore, claims 23-33, 35 and 37-42 have priority to 09/153,198 (9-15-98) and that therefore, the effective filing date of claims 31-33 is the filing date of parent application 09/153,198, which is 9-15-98.

Behr is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). The Examiner states without citation that Luciferase, which is a common marker gene, is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr is said to have

taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1 -19). The Examiner states that Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67). The phrase "transfecting antigen presenting cells" in the preamble is said not to bear patentable weight in considering the art *because it may not occur.* The Examiner then states, however, that the method of Behr *inherently results* in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). The examiner says that case has established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al., 186 USPQ 80 (CCPA). The Examiner admits that Behr did not teach the immunogenic protein was derived from a reverse transcriptase dependent virus.

However, Adachi is said to have taught a plasmid encoding replication-defective HIV used for transfecting a wide array of eukaryotic cells (pg 284, col. 2, 8 lines from the bottom; pg 285, col. 1, Table 1; pg 289, Table 2).

Response: No. Neither the molecular clone nor the virus particles were replication-defective.

Thus, the Examiner states that it would have been obvious for one of ordinary skill in the art at the time the invention was made to administer a complex of a plasmid encoding an immunogenic protein and PEI in a glucose solution to the skin/mucosa of an animal to express the protein in cells of the animal as taught by Behr wherein the plasmid encoded HIV proteins as taught by Adachi. One of ordinary skill in the art would have been motivated to use PEI to administer the plasmid of Adachi because PEI increased transfection as compared to DNA alone (Behr, col. 8, lines 13-19; col. 13, lines 6-10). One of ordinary skill in the art would have been motivated to replace the plasmid encoding luciferase with the plasmid encoding HIV proteins *to determine whether* an immune response against the HIV antigens would occur *in vivo*. One of ordinary skill in the art at the time the invention was made would have been motivated to use PEI to deliver DNA encoding HIV proteins because it was well known in the art at the time of filing that PEI could be used to deliver DNA encoding HIV proteins to cells (Owada, see pg 98, "Cells and Virus", "Compounds").

In response to the applicants' argument that the examiner's conclusion of obviousness is based on improper hindsight reasoning, the Examiner states that it must be recognized that any judgment of obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the invention was made, and does not include knowledge cleaned only from the applicants' disclosure, such a reconstruction is proper. See In Re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, the desire to replace luciferase protein with an HIV protein from replication-defective HIV would not require hindsight reasoning. One of ordinary skill in 1997 would have recognized that an attenuated HIV such as the replication-defective HIV of Adachi would prevent viral replication and death of the animal. One of ordinary skill in the art would also have recognized that attenuated HIV was desirable in a lab setting to add an extra measure of safety for lab technicians in case of accidental exposure.

The Examiner states that the applicants argue Behr relates to using PEI for gene therapy but does not specifically provide the requirements needed to apply a plasmid to the skin or mucosa such that APCs are targeted and transfected (paragraph bridging pg 21-22 of response filed 6-7-04). The Examiner states that the applicants' argument is not persuasive, because the phrase "transfecting antigen presenting cells does not bear patentable weight in considering the art *because it may not occur*. The Examiner states further that the body of the claim does not require transfecting APCs. Then, the Examiner states that the method of Behr inherently results in transfecting APCs, because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of

"dendritic cell", item 3). Methods of applying plasmids encoding antigens to the skin such that APCs were transfected were said to be known in the art (see Carson, US Patent 5,679,647; col. 36-37, Examples 11-12). Therefore, one of ordinary skill in the art at the time of filing would have had a reasonable expectation of successfully taking the teachings of Behr and transfecting APCs of the skin.

Applicants argue Adachi adds nothing to the Behr reference. The Examiner says Adachi teaches the replication-defective HIV in claim 38.

Applicants argue Owada does not address using PEI for delivering genes.

Applicants' argument is not persuasive. Owada need not teach all the limitations of the claims because Behr taught using PEI for delivering DNA encoding HIV antigens to the skin or mucosa *in vivo*. Owada provided additional motivation for one of ordinary skill in the art at -the time the invention was made to use PEI to deliver DNA encoding HIV proteins because Owada used PEI to deliver DNA encoding HIV proteins *in vitro*.

In response to applicants arguments against the references individually and "no linking teaching or guidance that would lead one of ordinary skill in the art to select the bits and pieces of the claimed invention from the voluminous options presented in the base reference" (pg 22, last 6 lines, of response filed 6-7-04), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir, 1986).

Response–Claims 23-38, 40 and 41

The applicants note that the present rejection is inapplicable to the amended Claims, at least because they relate to the transduction of antigen presenting cells *in vivo*, a limitation that is entitled to patentable weight. Because this limitation is missing, the basic requirements for establishing a *prima facie* case of obviousness have not been met. In addition, the experimental results in the references supplied herewith establish a therapeutic result has been obtained using the claimed method. In the Final Rejection bearing a mail date of September 22, 2004, the Examiner withdrew a claim limitation from consideration, refused to consider the experimental evidence that has been in the text of this case from September 15, 1998 and may have cited a new reference. That rejection was therefore a new rejection that was not required by a claim amendment. That rejection should not have been made final. MPEP 706.07(a). Further, no reason has been given for the extraordinary step of ignoring the inventors' experimental results. MPEP 707.07(l). Nor has any reason been given for this piecemeal approach to examination. MPEP 707.07 (g). The obligation of the Examiner is to make *valid* objections, and when those objections have been met, withdraw them.

Rejection under 35 USC §103

The present rejection does not establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or

combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art combination must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the expectation of success must be both found in the prior art, not in the applicant's disclosure. MPEP 2143.

The instant rejection does not meet these criteria.

First, the Examiner refuses to give patentable weight to a claim limitation, allegedly because it "may not occur," even though there is experimental support in the application text that it does occur, and then the Examiner proceeds to state that the references allegedly inherently teach that result, by cutting and pasting from very broad, nonspecific disclosures, then stating that one of ordinary skill in the art would be motivated to run an experiment with materials that the applicants disclose to have failed in other methods. Assuming that an experiment as described by the Examiner might be performable by one of ordinary skill in the art does not rise to the level of a teaching or suggestion to make the claimed combination plus the expectation of success that must be found in the prior art. MPEP 2143.01.

The Examiner does not cite any guidance to be found in either the base reference or the additional references, that would lead one of ordinary skill in the art to have a reasonable expectation that the claimed invention would work, or that the advantages of the claimed invention could be obtained.

Instead, the Examiner points to a motivation on the part of a hypothetical researcher to do an experiment, that is to determine whether an immune response would occur *in vivo*. That, at best, and assuming *arguendo* the teachings of the references are as clear as stated, would only mean that it would have been obvious to try the experiment. Obvious to try is not the standard of patentability. Rather, both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2143. The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) MPEP 2143.01.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein

operatively linked to a promoter. There is no teaching or suggestion anywhere in the prior art that the presently claimed method would work, or that its advantages could be obtained.

The Behr Reference

The Behr reference relates to the use of PEI as an adjuvant for gene therapy, preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4). Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration. The patent does not disclose how to target antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

This reference has disclosure consistent with that for a new material or a new use for a material with potentially wide application in a given field. What is beyond the scope of this reference is specific instruction as to how to realize the full potential of the material, that is, how to obtain the results that are potentially available from it, in areas that were not of direct interest to the inventors of the reference at the time.

The Adachi Reference

The Adachi reference reports the construction of an infectious molecular clone of HIV that was tested *in vitro* for the ability to produce infectious virus particles in a wide variety of cell lines. The disclosed method of transfection was calcium phosphate precipitation. It adds nothing to the Behr reference.

The Owada Reference

The Owada reference, "Enhancement of Human Immunodeficiency Virus Type 1 (HIV-1) Infection via Increased Membrane Fluidity by a Cationic Polymer" Microbiol. Immunol. 42(2), 97-107, Feb 1998, reports that PEI was screened as a drug *in vitro* for antiviral activity, and found to have some, but it was also shown to increase the rate of HIV-1 infection of CD4 cells by facilitating virus entry into the host cells. This reference does not address the use of PEI as a method of delivering genes at all, much less the claimed method of delivering genes into antigen presenting cells.

The Carson Reference

The Carson reference relates to a device for delivering "naked DNA," that is disclosed to be plasmid DNA encoding tumor-associated antigen. Examples 11-12 cited by the Examiner show that mice were vaccinated using a tyne device that is a device for intradermal injection, and had antibody responses. This reference does not disclose or discuss any method of transfecting antigen-presenting cells that relies a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, much less applying the complex to the skin or mucosa surfaces of an animal without an injection device.

Analysis

None of the cited references relate to the transfection of antigen presenting cells *in vivo*. The new, uncited reference relates to an injection method that requires a device. Neither the base reference nor the secondary references supply the specific information needed to make the claimed invention or show how the advantages of the claimed invention could be obtained. The combination does not meet the established criteria for rendering the claimed invention obvious. Even if the uncited reference were added to the combination, the claimed invention would not result because the uncited reference relates to an injection device. One of the advantages of the present invention is that no such devices are required. (See application page 25, line 14).

Further, there is no linking teaching or guidance that would lead one of ordinary skill in the art to select the rest of the bits and pieces of the claimed invention from the voluminous options presented in the base reference. The secondary and tertiary references at best supply materials that are cumulative to the base reference, but they do not have

anything to say about the claimed method. That is, they do not fill the gaps in the base reference. This rejection should be withdrawn at this time. The Examiner's charge that the applicants have attacked the references individually only and not addressed the combination is factually incorrect. The applicants have shown that the there is no linking teaching or guidance to make the combination. That is a basic requirement for the rejection that has not been met. The use of headers to clarify the scope and content of individual pieces of prior art is a tool to provide clarity, not an impermissible attack on the references individually. The teachings are not in the references, and so the combination cannot be made. The *prima facie* rejection is defective and should be withdrawn.

6. Claim Rejections – 35 USC § 103

Claims 23-33, 35, and 37- 41

Claims 23-33, 35, and 37-41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol.. 59, pages 284-291) and Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97-107) as applied to claims 23-38, 40 and 41, further in view of Holler (US Patent 5,908,923).

The Examiner states that the combined teachings of the Behr, Adachi and Owada references taught a complex comprising i)- PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding a protein from a replication-defective HIV operatively linked to a promoter suspended in 5% glucose (see 103 rejection above). The Examiner admits that the combined teachings of the Behr, Adachi, and Owada references did not teach the protein from replication-defective HIV was from integrase defective HIV.

The Examiner states that, however, the Holler reference taught a plasmid encoding replication-defective HIV that was integrase defective for use *in vivo* (col. 4, lines 51-54).

The Examiner concludes that it would have been obvious for one of ordinary skill in the art at the time the invention was made to administer a complex of a plasmid encoding an HIV protein and PEI in a glucose solution to the skin/mucosa of an animal to express the protein in cells of the animal as taught by the combined teachings of Behr, Adachi and Owada wherein the plasmid encoding HIV proteins was integrase defective as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV integrase defective to prevent causing disease in the animal.

The Examiner remarks that the Applicants argue Holler merely teaches that the replication-defective, integrase defective H IV is usable but does not say anything about the claimed method. The Examiner says that the Applicants suggest Holler recommends that the gene can be successfully delivered by any method. However, the parent application (please refer to the instant application) cites Arthur and Song who both state only "low efficient" in vitro methods were known at the time. The Examiner states that the Applicants' argument is not persuasive, because Song is said to have taught APCs were successfully transfected with plasmid encoding HIV and that the APCs presented HIV antigens (pg 1946, col. 1, "Dendritic cell fraction contains antigen-presenting cells that can prime naive T-cells in vitro"). Song taught administering retroviral particles encoding HIV 11113 env/rev to mice intramuscularly (pg 1943, col. 2, "Retroviral vectors" and "Immunizations...") or with dendritic cells transduced with the virus injected intraperitoneally (pg 1943, col. 2, "Retroviral vectors" and "Immunizations..."). Even if transfection efficiency was low (which has not been supported by applicants), the method of Song was a success. The teachings of Arthur have not been provided and are not of record. Holler provides a reasonable expectation of success because Holler transfected CEM (a

lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would still have a reasonable expectation of successfully transfecting APCs as claimed with the modification taught by Holler.

In response to applicants arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 23-41 – Response

Rejection under 35 USC §103

As discussed above, the combined teachings of the Behr, Adachi and Owada references did not teach the claimed method. To the extent Holler teaches a replication-defective HIV, the applicants point out that the reference is cumulative of other references cited in the background of the application. The Owada reference does not repair the defects in the attempted case of *prima facie* obviousness because it does not contain any suggestion or instruction as to how to pick and choose through the very broad disclosure of the base reference, or any of the other references, to make the claimed invention. It simply adds another raw material. The Applicants point out that the teachings of the references are by no means so clear and precise as they appear in the Examiner's summary, because the Examiner, guided only by the teachings of the Applicants, has used snippets and short quotes selected from the base reference to piece together the rejection. This is a classic case of hindsight reconstruction of a claimed invention based only on the Applicant's disclosure, and the citation of other references from the background of this application do not change that fact. The Federal Circuit has required that, in order to avoid hindsight reconstruction, the Examiner must point to guidance, or connecting teaching outside that provided by the Applicants to suggest that the claimed combination should be made. The Examiner does not cite any guidance to be found in either the base reference or the additional references, that would lead one of ordinary skill in the art to make the selections that would lead to the invention, have a reasonable expectation that the claimed invention would work, or that the advantages of the claimed invention could be obtained.

Instead, the Examiner points to a motivation on the part of a hypothetical researcher to do an experiment. That, at best, and assuming *arguendo* the teachings of the references are as clear as stated, would only mean that it would have been obvious to try the experiment. Obvious to try is not the standard of patentability. Rather, both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the

prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) MPEP 2143.01. With the preceeding paragraphs opening the discussion, and the closing summary paragraph below, it is not seen how the Examiner can claim that the applicants have merely argued against the references individually. The use of headers to show where the scope and content of the prior art is being discussed is a device directed to clarity, and does not convert an analysis of an obviousness rejection in the classic format to an attack limited to the references individually.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. There is no teaching or suggestion anywhere in the prior art that the presently claimed method would work, or that its advantages could be obtained.

The Scope and content of the Behr, Adachi, and Owada References are discussed in the immediately preceeding rejection under 35 USC § 103

In brief, they do not disclose the claimed method of transfecting antigen presenting cells *in vivo*.

USPN 5,908,923 to Holler, et al.

The Holler reference discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection. All of the The Examiner states that the reference teaches a plasmid encoding a replication-defective HIV that was integrase defective for use *in vivo* based on the disclosure from Col. 4, lines 51-54. The disclosure is quoted in full below.

> Thus, in a tenth aspect, the present invention is directed to a method of treating AIDS in a patient comprising administering to said patient a therapeutically effective amount of a transdominant negative integrase gene. Col. 4, lines 51-54.

There are no *in vivo* examples in this reference.

The applicants point out that this disclosure simply amounts to a suggestion that the gene is useable. It says nothing about the claimed method. Indeed, this 1994 reference would appear to recommend that the gene can be successfully delivered by any and all methods. See Col. 7 lines 40-57. However, the present application discloses that an article

published several years later reported only "low efficient" *in vitro* methods were known at the time, see page 6, lines 4-11 (cites to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997); and that neither they nor the known *in vivo* methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells. See page 6, lines 16-19. Thus, this reference adds nothing to the cited combination.

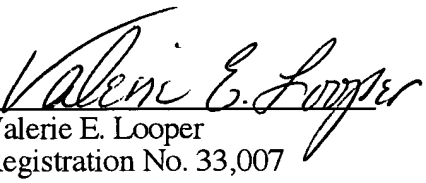
The Examiner has stated that the applicants' comment that the Holler reference recommends the gene can be successfully delivered by any method, and that this is not persuasive because certain "low efficient" methods cited in the background section of the present application were said to be "successful." This argument misses the point. The reference does not teach the claimed method, and it is the method, not the raw materials, that is lacking in the prior art. Christening the prior art "successful" when it was not, doesn't change the fact that the new method is not disclosed in the prior art. The reference does not differentiate among methods of gene delivery, or provide any basis to choose the present method from among many, successful or not. The claimed invention is not a given retrovirus, nor is it an adjuvant. It is a method of transfecting antigen presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

In the Final Rejection bearing a mail date of September 22, 2004, the Examiner withdrew a claim limitation from consideration, refused to consider the experimental evidence that has been in the text of this case from September 15, 1998, and cited new art that was not required by a claim amendment. That rejection was therefore a new rejection that was not required by an amendment made by the applicants, and should not have been made final. MPEP 706.07(a). Further, the characterization of the Applicants' response to the prior rejection as merely attacking the references individually is incorrect. The structure of the response to the rejection is in the classic format: introductory paragraph summarizing why the combination is incomplete; discussion of the applicable law; scope and content of each of the references, specifically pointing out what is missing and why; and a conclusion. The use of headers to specifically point out the sections relating to each piece of prior art does not convert this full, legally appropriate and factually supported response into an attack on the references individually.

Conclusion

For all the above reasons and amendments, it is believed that the Examiner's concerns have been fairly met. Favorable consideration is solicited.

Respectfully Submitted,



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